Shiny White Patches of the Arms and Forehead

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Case Report

A 45 year-old African-American woman with a past medical history significant for human immunodeficiency virus (HIV) on highly active antiretroviral therapy (HAART) presented with "shininess" and "whitening" of both arms and forehead over the past three years. She was diagnosed as having "dermatitis" by an outside dermatologist and tried various topical steroid creams, ammonium lactate cream, and ketoconazole cream without any relief. She denied any family or personal history of any skin diseases or autoimmune disease including Raynaud's phenomenon. Review of systems was positive for recent weight loss of greater than 10 pounds over two months, joint pain, hair loss, and stomach upset. The patient also reported worsening pruritus. On physical examination, there were multiple hypopigmented macules and patches (leukoderma) on the arms, thighs, and frontal hairline (Figure 1). The skin was noted to be poikilodermatous diffusely, there was absence of facial wrinkling, and dilated capillary loops were seen surrounding all fingernail cuticles (Figures 2 and 3). The arms and legs appeared to be mildly edematous and had a boggy texture with loss of hair. Decreased hair density with perifollicular inflammation and hypopigmentation as well as loss of follicular ostia was appreciated in areas affecting the frontal and temporal scalp. A punch biopsy of the left thigh was performed and sent for histological analysis. Blood examination was also conducted.

Diagnosis

Scleroderma/systemic sclerosis (SSc)

Microscopic Findings and Clinical Course

Histological analysis of the left thigh revealed a normal epidermis and a thickened, homogenized dermis with acellular fibrosis and diminution of adnexae (Figures 4A and 4B). An Alcian blue stain was performed and revealed increased dermal mucin (Figure 5). Blood examination demonstrated serum anti-nuclear antibody (ANA) elevation at 1:640 with a nucleolar pattern, but failed to demonstrate anti-topoisomerase (Scl-70), anti-centromere, anti-fibrillarin, or anti-ribonucleoprotein antibodies. The patient was referred to rheumatology, cardiology, pulmonology, and nephrology for evaluation. She was started on weekend only topical clobetasol ointment and topical calcipotriene cream twice daily for lesions of the body and scalp. Oral hydroxyzine and topical Gold Bond Maximum Relief Anti-Itch Cream (dimethicone/pramoxine) was given for itching and sleep disturbance, oral simvastatin and aspirin for Raynaud's prevention, oral omeprazole for reflux symptoms, and oral acetaminophen as needed for joint pains.

Discussion

Scleroderma or SSc is used to describe a rare systemic autoimmune disease characterized by skin induration and thickening, fibroproliferative vasculopathy, chronic inflammatory infiltration in numerous visceral organs, and humoral and cellular immune alterations (production of auto-antibodies). SSc encompasses a broad spectrum of clinical presentations that range from localized skin changes (morphea) to multisystem involvement (SSc).[1] The American College of Rheumatology set forth criteria for the classification of SSc in 1980 in which qualifying patients met one major and two minor criteria.[2] Evidenced-based research has revealed new information in the pathophysiology of the disease helping to define more sensitive criteria in 2001 (Table 1).[3] Updates to the current criterion are underway in order to reflect more recent advances in laboratory and clinical research (Table 2).[4] The abnormal capillary nail pattern, swollen-appearing extremities, and

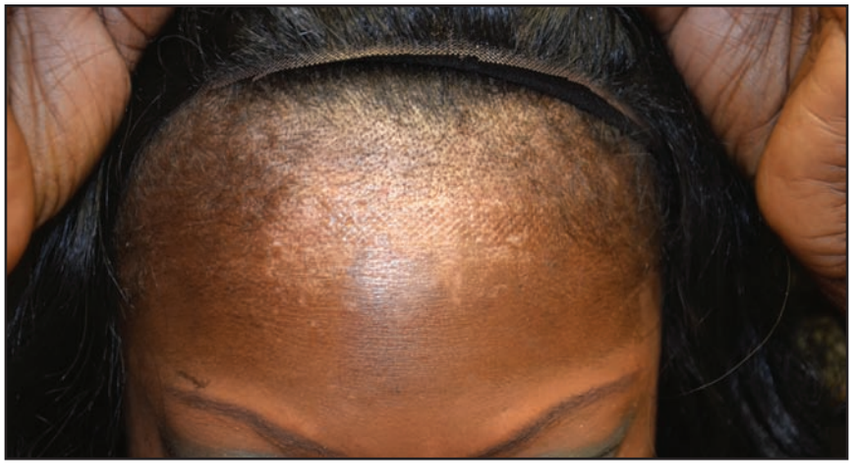


Figure 1. Leukoderma of the frontal hairline with surrounding decreased hair density

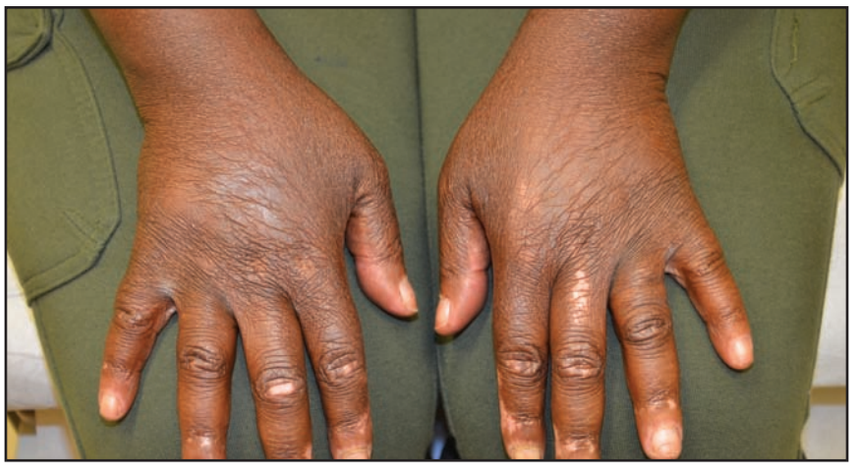


Figure 2. Diffuse poikiloderma on the dorsal hands

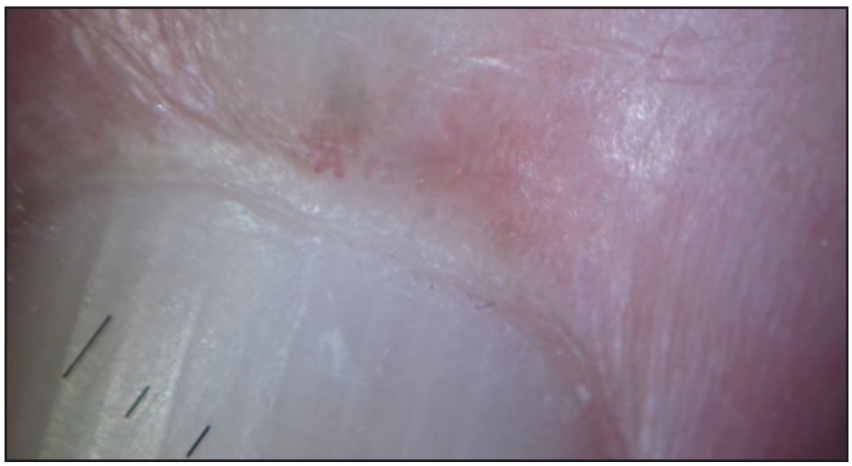


Figure 3. Nailfold capillaroscopy demonstrating dilated vascular loops

lack of facial rhytides are important diagnostic findings in this case.

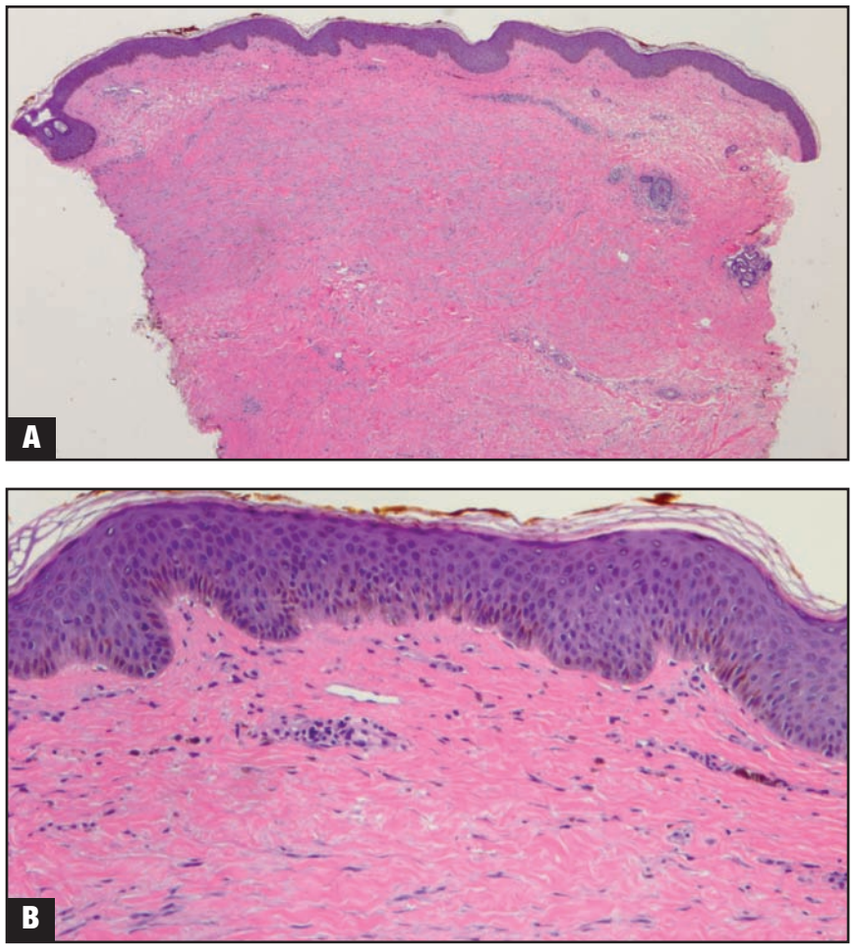
Localized disease can manifest as linear scleroderma, en coup de sabre, or morphea. Linear scleroderma commonly presents in childhood with induration and fibrosis often in a band-like, unilateral, or dermatomal distribution that has the potential to cross joints. This can lead to severe functional morbidity including contractures that limit movement and require physical therapy or surgery (Figure 6).[5] When manifesting on the face or scalp, it is termed en coup de sabre, aptly named for its saber strike-like appearance. Atrophy of skin, muscle, and bone may consequently advance to neurological and ophthalmological dysfunction (Figure 7). Morphea can present with localized patches or large symmetrical sclerotic patches on the trunk or extremities (Figure 8).[6]

The classification of SSc requires both skin and visceral involvement. Raynaud's phenomenon is found in nearly all forms and may be present for several years prior to fibrosis. Periungual vascular changes in the nailfold, including enlarged capillaries and/or capillary loss with or without perivascular hemorrhages are commonly seen.
Fingertip ulcers, pitting scars, flexural contractures, as well as acroosteolysis may also be present (Figure 9). In the CREST variant, patients may exhibit limited cutaneous disease, but also have calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia. A thorough history and physical exam, serum calcium and phosphate levels, the presence of positive ANA titers, and exclusion of thyroid disease are essential. Leukoderma may be an initial cutaneous finding suggestive of

systemic or generalized involvement (Figure 10). In patients with generalized morphea, vascular symptoms and internal organ involvement are ordinarily absent and there is sparing of the hands and face.

The visceral pathology associated with SSc is largely due to persistent vascular injury resulting in chronic tissue damage. Structural changes in vessels can advance to permanently impaired blood flow causing ischemia and fibrosis. Although a thorough history may reveal or help to rule out systemic involvement, all patients diagnosed with generalized cutaneous disease should be evaluated with laboratory and diagnostic testing for systemic involvement. Of importance, the gastrointestinal system is frequently affected. Although fibrosis of smooth muscle can occur anywhere in the digestive tract, esophageal involvement is most common, manifesting as dysphagia, chronic reflux, and aspiration.[7] Pulmonary disease is characterized by diffuse fibrosis leading to arterial hypertension. Vasculopathy in the kidneys can cause azotemia and systemic hypertension. Renal crisis is encountered in approximately 15 percent of SSc patients and is characterized by acute oliguria and proteinuria.[8] Cardiac involvement may result as a consequence of direct arterial damage or be secondary to pulmonary and/or systemic hypertension.[9]

The histopathological characteristics of SSc depend on the stage of the biopsy taken. Early lesions are characterized by edema of the reticular and papillary dermis and may be indistinguishable from scleredema of Buschke.[10,11] Inflammation composed of histiocytes, lymphocytes, and plasma cells are present perivascularly and at



Figures 4A and 4B. Histological analysis of the left thigh with normal epidermis and a thickened, homogenized dermis with acellular fibrosis and diminution of adnexae (H&E 2x and 10x)

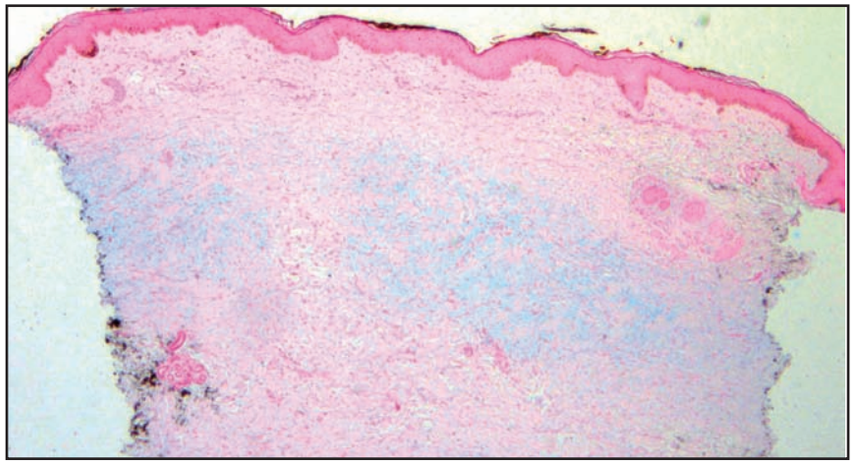


Figure 5. An alcian blue stain revealing increased dermal mucin

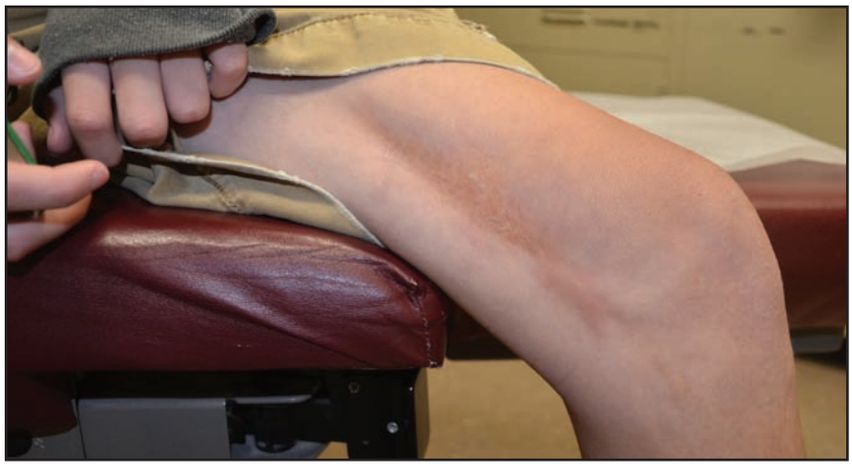


Figure 6. Linear scleroderma commonly presents in childhood with induration and fibrosis often in a band-like, unilateral, or dermatomal distribution

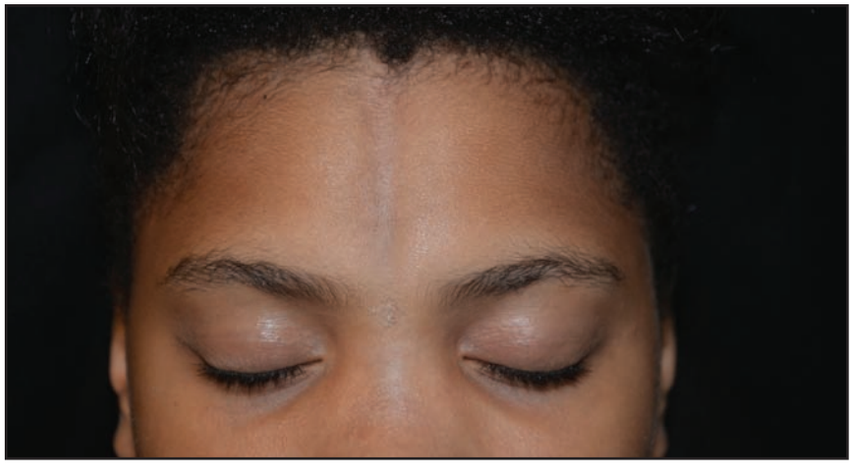


Figure 7. En coup de sabre, aptly named for its saber strike-like appearance

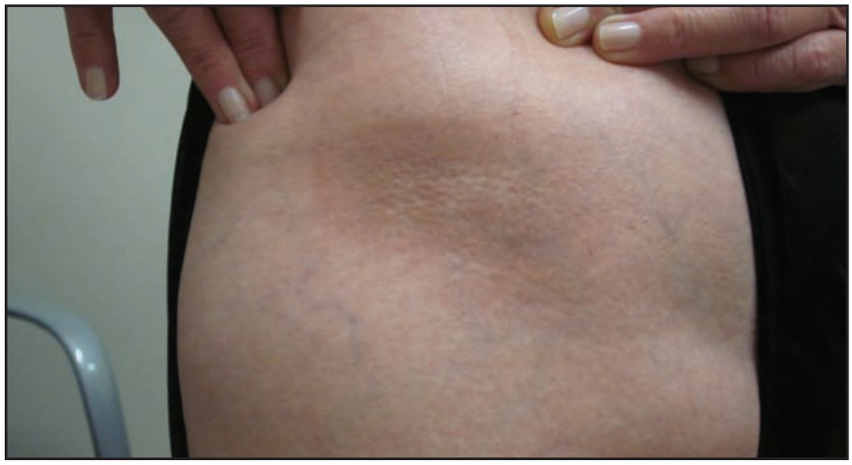


Figure 8. Morphea may either present with localized patches of sclerotic skin or with large, often symmetrical patches on the trunk or extremities

the boundary between the dermis and subcutaneous fat.[12,13] In later stages, the epidermis is spared or there may be an effaced rete ridge pattern (atrophy). Further progression demonstrates pan-dermal sclerosis with fibrosis continuous with the panniculus, giving the biopsy a "square" or "box-car" appearance. Subcutaneous fat lobule obliteration and collagen deposition in and around eccrine glands is seen.[14,15] The collagen is hyalinized and homogenous, extending from the papillary dermis to the subcutis and entraps adnexal structures.[14] Elastic fibers are unaffected. More significant inflammation is seen in other autoimmune connective tissue diseases, such as systemic lupus erythematosus (SLE) as compared to SSc. Immunoglobulin deposition at the dermoepidermal junction and within small blood vessels is uncommon in SSc, but more frequent in SLE. Pan-dermal sclerosis and fibrosis is common in SSc, but uncommon in other autoimmune connective tissue diseases, such as SLE where interface dermatitis and mucin deposition are more characteristic findings.[15]

Localized scleroderma or morphea cannot be histologically distinguished from SSc. Epidermal changes and dense inflammation are more common in morphea.[13] Lichen sclerosus et atrophicus (LS) is distinguished by liquefactive degeneration of the basal layer and a dense lichenoid infiltrate similar to SLE, which is not present in localized scleroderma. Papillary dermal edema, which is commonly found in early stage SSc, is frequent in LS.

Serological tests consisting of ANA screening with highly specific (>99.5%) assays for anti-DNA topoisomerase I (anti-Scl-70) antibodies, anti-centromere antibodies, and anti-RNA polymerase III antibodies are indicated in patients

with suspected disease.[17] Blood examination is useful in differentiating between the localized and systemic disease subtypes and determining prognosis. The presence of anti-centromere antibodies is more frequently documented in cases of limited cutaneous disease (CREST) and positive titers of Scl-70 antibodies are likely in diffuse disease and interstitial lung involvement.[18] Patients with positive anti-RNA polymerase III antibodies have been found to have a higher risk of early renal crisis as well as rapidly progressive skin disease.[19] If serology is indicative of a connective tissue disease in conjunction with scleroderma-like symptoms, an overlapping syndrome can be considered as a possible diagnosis and further rheumatological work-up is indicated.[3]

Basic hematological analysis including a complete blood count with differential and comprehensive metabolic panel should be performed to look for anemia and renal or liver disease respectively. Urinalysis including microproteins and cast assessment should be performed. Nonspecific assays of inflammation, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may also be helpful when assessing treatment efficacy after a diagnosis is confirmed. A recent evaluation of patients with SSc documented a poorer prognosis in patients with an elevated initial ESR.[20] Serum muscle enzymes including creatinine kinase (CK), aldolase, lactate dehydrogenase (LDH), and aminotransferases may be elevated in cases of scleroderma-induced myositis and in other autoimmune conditions, such as dermatomyositis (DM) or polymyositis. Raynaud's phenomenon and scleroderma-like nailfold capillary abnormalities may be seen in other conditions, such as DM and polyarteritis nodosa (PAN). However, DM has distinctive skin findings, such as violaceous periorbital rash (heliotrope rash); symmetric erythematous papules and plaques of the extensor surfaces of the interphalangeal (IP), metacarpophalangeal (MCP), elbow and/or knee joints (Gottron's sign); and confluent flat erythematous patches of the shoulders, neck, and anterior chest (Shawl sign). Poikilodermatous patches/plaques of the lateral thighs (Holster's sign) may give a similar appearance to morphea or early cutaneous leukoderma seen in SSc, as well as LS. Cutaneous manifestations of PAN include tender subcutaneous nodules, palpable purpura, and livedo reticularis that are not typical of SSc. Hypothyroidism, chronic renal disease, amyloidosis, graft-versus-host-disease, toxic oil syndrome, mycosis fungoides, eosinophilia–myalgia syndrome, and eosinophilic fasciitis, may all be associated with scleroderma-like skin

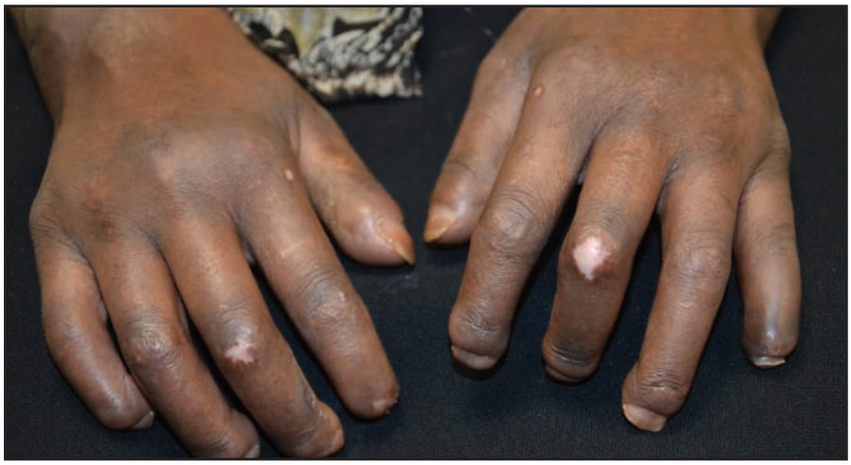


Figure 9. Fingertip ulcers, pitted scars, and flexural contractures of systemic sclerosis

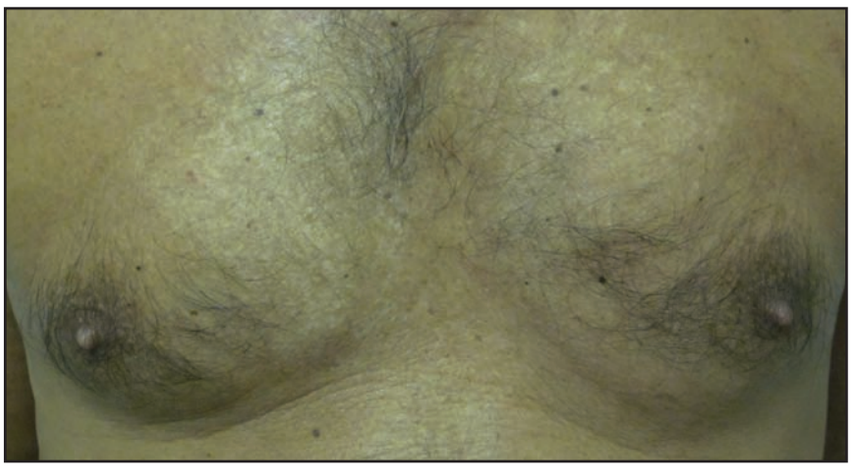


Figure 10. Leukoderma may be an initial cutaneous finding suggestive of systemic sclerosis

changes and should be considered in the differential diagnosis. Scleroderma can also result from chronic environmental exposure to resins, organic solvents, or pesticides, as well as from traumatic occupational insult such as vibration (jackhammering).[21]

There is a paucity of therapeutic clinical trial data in patients with SSc, in part due to a relatively low frequency of occurrence and a wide range of clinical variability.[22] Further, there are no official United States Food and Drug Administration (FDA) approved therapies for SSc. In general, therapy aimed at reducing inflammatory activity in early disease is more successful than attempts to decrease sclerosis in well-established lesions. Treatment is guided by involvement, location, and extent of disease determined by a thorough history and physical exam and laboratory and diagnostic testing.

For morphea or localized scleroderma, topical, intralesional or oral corticosteroids, topical vitamin D preparations (calcipotriene, calcitriol), topical calcineurin inhibitors (pimecrolimus, tacrolimus), topical imiquimod, and/or lesion-directed phototherapy are first line.[23,24] In one case report, treatment of plaque-type morphea with the 585nm pulsed dye laser led to substantial improvement.[25] Photodynamic therapy and intralesional interferon-gamma have been tried without success.[26-28]

Patients with potentially disabling generalized, linear, or deep morphea require more aggressive therapy with systemic corticosteroids (oral or intravenous pulse therapy) and/or methotrexate.[29-32] Other systemic medications have been tried with varying efficacy, such as mycophenolate mofetil, azathioprine, D-penicillamine, cyclosporine, and hydroxychloroquine. [33]

Treatment of generalized or systemic disease is more difficult. Long-wavelength ultraviolet A1 (UVA1; 340-400nm) may be beneficial given its deeper skin penetration versus low-dose broadband UVA (320–400nm).[34] Narrowband ultraviolet B (NBUVB; 311–312nm) is less potent given its limited dermal penetration. Phototherapy is a beneficial treatment option for refractory or severe disease due to its minor adverse effect profile as compared with immunosuppressive agents. Plamsapheresis and photophoresis as well as immunosuppressive medications, such as cyclophosphamide, oral corticosteroids, cyclosporine, methotrexate, mycophenolate mofetil, and rituximab (anti-CD20), have all demonstrated efficacy.[33] Therapies that may serve to slow the progression of fibrosis and are not immunosuppressive include colchicine and D-penicillamine, a chelating agent that cleaves newly formed crosslinks from dermal collagen.[35] Intravenous iloprost, a synthetic analog of prostacyclin, may help to improve fibrosis and reduce periungual vascular changes by suppressing connective tissue growth factor in fibroblasts.[36,37] Imatinib, a tyrosine kinase inhibitor, has also shown promise as an antifibrotic agent due to its activity against c-Abl, platelet-derived growth factor (PDGF) receptor, and other tyrosine kinases involved in transforming growth factor beta (TGFβ) and PDGF signaling, which are implicated in controlling processes of cellular differentiation, division, adhesion, and stress responses.[38] Allogeneic bone marrow transplantation has been shown effective in uncontrolled studies.[39] For associated skin pruritus, oral antihistamines, tricyclic antidepressants (doxepin), and trazodone may be beneficial and improve sleep disturbances.

For calcinosis cutis, many treatments have been reported with varying success, including warfarin, bisphosphonates, minocycline, ceftriaxone, diltiazem, aluminium hydroxide, probenecid, intralesional corticosteroids, intravenous immunoglobulin, curettage, surgical excision, carbon dioxide laser, and extracorporeal shock wave lithotripsy.[40] The author (JE) has found success with a combination of an oral bisphosphonate, colchicine, and diltiazem in mild disease. Intralesional corticosteroid injections in combination with 5-fluorouracil (ratio 1:9) with or without extracorporeal shock wave lithotripsy or surgical removal have been beneficial in patients with large localized or ulcerative disease. A recent case report documented significant improvement with the use of rituximab (2 courses, consisting of 4 weekly infusions, 375mg/m^2 each) of CREST-related calcinosis and the associated pain accompanying it.[41]

Those with Reynaud's phenomenon should be counseled to avoid extremes in temperatures (specifically cold), smoking, caffeine, nicotine, stress, and pseudoephedrine (oral stimulants). Reported treatments include topical nitroglycerin, α1-antagonists (prazosin), calcium channel blockers (nifedipine), dipyridamol, sildenafil, losartan, prostaglandin E1, aspirin, pentoxifylline, and injectable botulinum neurotoxin A.[42,43] In a review of randomized clinical trials, prostacyclins, such as iloprost or epoprostenol, were found to be the most effective therapeutic options.[44] In the event of thrombosis and vascular flow compromise, a tissue

plasminogen activator, heparin, or urokinase may be necessary. The author (JE) begins all patients on an oral cholesterol-lowering agent, such as a statin to prevent microvascular atherosclerosis, as well as a low-dose aspirin and/or pentoxifylline to help improve peripheral vascular perfusion.

Angiotensin converting enzyme (ACE) inhibitors are recommended in the management of hypertension and SSc renal crisis.[45] The addition of other classes of antihypertensive medications, such as calcium channel blockers may be required to maintain optimal control of blood pressure. Prokinetic agents, such as erythromycin, cisapride, or metoclopramide may aid with gastrointestinal dysmotility. Empiric use of proton pump inhibitors or histamine blockers may prevent stricture formation. Octreotide may be necessary in severe cases of gastrointestinal disease.[46]

Pulmonary fibrosis is treated with prednisone, cyclophosphamide or other immunosuppressive agents, such as methotrexate, cyclosporine, or mycophenolate mofetil. Bosentan, an endothelin-1 receptor antagonist that is approved to treat pulmonary artery hypertension (PAH), has also been shown to improve digital ischemia and ulceration given its vasodilatory and antifibrotic effects.[47,48] Sildenafil and prostacyclin analogs may also improve PAH.[49,50]

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DIAGNOSTIC DILEMMAS IN DERMATOLOGY